

**Standard treatment options:**

Treatment of patients with stage IV endometrial cancer is dictated by the site of metastatic disease and symptoms related to disease sites. For bulky pelvic disease, radiation therapy consisting of a combination of intracavitary and external-beam radiation therapy is used. When distant metastases, especially pulmonary metastases, are present, hormonal therapy is indicated and useful.

The most common hormonal treatment has been progestational agents, which produce good antitumor responses in as many as 15% to 30% of patients. These responses are associated with significant improvement in survival. Progesterone and estrogen hormone receptors have been identified in endometrial carcinoma tissues. Responses to hormones are correlated with the presence and level of hormone receptors and the degree of tumor differentiation. Standard progestational agents include hydroxyprogesterone (Delalutin), medroxyprogesterone (Provera), and megestrol (Megace).[1]

Several randomized trials by the Gynecologic Oncology Group have utilized the known antitumor activity of doxorubicin. The addition of cisplatin to doxorubicin increased response rates and progression-free survival (PFS) over doxorubicin alone but without an effect on overall survival (OS).[2] However, in a trial conducted in a subset of patients with stage III or IV disease with residual tumors <2 cm and no parenchymal organ involvement, the use of the combination of cisplatin and doxorubicin resulted in improved OS compared to whole-abdominal radiation therapy (adjusted hazard ratio = 0.68; 95% confidence interval limits, 0.52-0.89;  $P = .02$ ; 5-year survival rates of 55% vs. 42%).[3] [Level of evidence: 1iiA] In a subsequent trial, paclitaxel with doxorubicin had a similar outcome to cisplatin with doxorubicin.[4,5] The 3-drug regimen (doxorubicin, cisplatin, and paclitaxel) with granulocyte colony-stimulating factor, however, was significantly superior to cisplatin plus doxorubicin: response rates were 57% versus 34%, PFS was 8.3 months versus 5.3 months, and OS was 15.3 months versus 12.3 months, respectively. The superior regimen was associated with a 12% grade 3 and a 27% grade 2 peripheral neuropathy.[4,5] [Level of evidence: 1iiDiii]

EXHIBIT C